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Efficacy and safety of statin therapy in older people: meta-analysis of individual participant data from 28 randomised controlled trials

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Abstract

Background

Statin therapy has been shown to reduce major vascular events and vascular mortality in a wide range of individuals, but there is uncertainty about its efficacy and safety among older people.

Methods

Randomised trials of statin therapy were eligible if they aimed to recruit at least 1000 participants with scheduled treatment duration of at least 2 years. Individual participant data from 22 trials (n=134,537) and detailed summary data from one trial (n=12,705) of statin therapy versus control, plus individual participant data from 5 trials of more-intensive versus less-intensive statin therapy (n=39,612), were analysed. Participants were subdivided into age groups: ≤55 years; >55≤60 years; >60≤65 years; >65≤70 years; >70≤75 years; and >75 years. Effects on major vascular events (ie, major coronary events, strokes and coronary revascularisations), cause-specific mortality and cancer incidence were estimated as the rate ratio (RR) per 1.0 mmol/L (39mg/dL) LDL cholesterol reduction.

Findings

Among 186,854 participants in 28 trials, 14,483 (8%) were aged above 75 years at randomisation. Median follow-up duration was 4.9 years. Overall, statin/more therapy produced a proportional reduction in major vascular events of 21% (RR 0.79; 95% CI 0.77-0.81) per 1.0 mmol/L reduction in LDL cholesterol. Although the proportional reductions in major vascular events appeared to diminish slightly with age, the trend was not significant (trend p=0.06) and there was significant benefit in all age groups. With increasing age, there was a trend towards smaller risk reductions in major coronary events (trend p=0.009), but not in coronary revascularisation procedures (trend p=0.6) or stroke (trend p=0.7). After exclusion of 4 trials which enrolled only patients with heart failure or undergoing renal dialysis (among whom statin therapy has not been shown to be effective), the trend persisted for major coronary events (trend p=0.01), but remained non-significant for major vascular events (trend p=0.3). The proportional reduction in major vascular events was similar, irrespective of age, among patients with pre-existing vascular disease (trend p=0.2), but appeared smaller among older individuals not known to have vascular disease (trend p=0.05). There was a trend (p=0.004) towards smaller proportional reductions in vascular mortality with older age, but this did not persist after exclusion of the heart failure or dialysis trials (trend p=0.2). Statin therapy had no effect at any age on non-vascular mortality, cancer death or cancer incidence.

Interpretation

Statin therapy produces significant reductions in major vascular events irrespective of age, but there is less direct evidence of benefit among patients aged over 75 who do not already have evidence of occlusive vascular disease; this limitation is now being addressed by further trials.

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Introduction

Meta-analyses of individual participant data from 27 randomised trials in the Cholesterol Treatment Trialists' (CTT) Collaboration database indicate that each 1.0 mmol/L reduction in LDL cholesterol with statin therapy reduces the risk of major vascular events by about one fifth, with similar proportional risk reductions among men and women,[1] a[1]nd across different levels of absolute risk.[2] However, even among patients with established cardiovascular disease, utilisation rates of statin therapy have been shown to decline with increasing age, and are significantly lower in people aged over 75 years, reflecting differences in both prescribing and compliance.[3,4] This trend is even more prominent among older patients who do not have evidence of occlusive vascular disease.[5] One explanation may relate to uncertainty about applying the evidence for statin efficacy and safety from randomised trials to an elderly population, given that a relatively small number of people aged over 75 were enrolled in such trials, and many elderly people have non-cardiovascular comorbidities.[6-10] The CTT collaboration has age-specific data on vascular events, cause-specific mortality and cancer from 28 randomised controlled trials of statin therapy among a total of nearly 187,000 participants, of whom about 14,500 were aged over 75 at baseline. Consequently, it is uniquely placed to help address uncertainties about the effects of statin treatment among older individuals.

Methods

Study Design

Methods were pre-specified in a CTT collaboration protocol published prior to the reporting of any individual trial results.[11] Randomised trials were eligible for inclusion if: (i) the main effect of at least one of the trial interventions was to lower LDL cholesterol; (ii) the trial was unconfounded with respect to this intervention; and (iii) the trial aimed to recruit 1000 or more participants with scheduled treatment duration of at least 2 years.[11] As for all CTT analyses,[1,2,11-16] the risk of bias was low owing to: pre-specified study methods; the ability to adjust for heterogeneity by weighting rate ratios according to trial-level absolute differences in LDL cholesterol; and the low probability of publication bias due to a prospective design with pre-specified study eligibility. Pre-specified outcomes included major coronary events (defined as non-fatal myocardial infarction (MI) or coronary death), coronary revascularisation (angioplasty or bypass grafting), stroke (subdivided by type), site-specific cancers and cause-specific mortality. Subsequently, major vascular events were defined as the composite of major coronary events, coronary revascularisation and stroke. Pre-specified sub-group analyses included comparisons of the effects of statin therapy among people

aged ≤65 and >65 years at randomisation (along with several other subgroupings, including by history of vascular disease).[11 11]For the present analyses, we compared effects between six age groups (≤55, >55 to ≤60, >60 to ≤65, >65 to ≤70, >70 to ≤75 and >75 years) and, where statistical power was limited, between two retrospectively-defined groups (≤75 and >75 years). Due to a disproportionate representation of older people (particularly aged >75 years) in trials conducted exclusively among people with heart failure[17,18] or receiving renal dialysis,[19,20] for whom statin therapy shows little or no benefit, we also examined the effects after excluding these trials.

Statistical Analysis

The meta-analysis was conducted according to the intention-to-treat principle, using the same methods described previously.[11,12,14] Results are presented as rate ratios per 1.0 mmol/L reduction in LDL cholesterol. [1,2,12-16]Proportional risk reductions in different age subgroups were compared using standard χ^2 tests for heterogeneity when there were two groups, or trend when there were more than two groups. To allow for multiple subdivisions of the data into subgroups, only summary rate ratios are presented with 95% CIs; all other rate ratios are presented with 99% CIs. All analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA) and R version 3.2.5.

Role of the funding source

No funding source had any role in study design, data collection, data analysis, data interpretation or writing of this manuscript. The writing committee had full access to all the data in the study and take final responsibility for its content.

Results

Individual participant data were provided by investigators or sponsors for 27 trials of statin therapy, and one further trial[21] provided detailed summary data, permitting meta-analyses of all 28 trials. Twenty three trials investigated the effects of statin therapy vs. control (147,242 participants; median follow-up 4.8 years) and five trials compared more intensive versus less intensive statin therapy (39,612 participants; median follow-up 5.1 years).[1] Data were not available for four eligible trials (9,264 participants), all of which exclusively enrolled people with known vascular disease.[22-25] The median follow-up duration was 4.9 years, ranging from 2.0 years to 7.0 years. Of the 186,854 participants, 39,242 (21%) were aged ≤55, 31,434 (17%) were aged >55 to ≤60, 37,764 (20%) were aged >60 to ≤65, 36,567 (20%) were aged >65 to ≤70, 27,314 (15%) were aged >70 to ≤75 and 14,483 (8%) were aged>75 years (webtable 1; age was unrecorded for 50 participants).

There were significant differences in each of the measured baseline characteristics across the six age groups ($p<0.001$ for all comparisons; webtable 2). In particular, older participants were more likely to be female and to have heart failure or hypertension, and less likely to be current smokers. Patients included in heart failure trials comprised 20% of those aged >75 years compared to 4% of those aged ≤75 years; and patients in renal dialysis trials comprised 4% of patients aged >75 years compared to 2% of those aged ≤75 years (Table 1). There was a trend towards lower baseline LDL cholesterol concentrations with increasing age in the statin vs control trials and, to a lesser extent, in the more vs less statin trials. Mean LDL-cholesterol differences between treatment arms at one year (overall difference 1.08 mmol/L) were slightly smaller among older participants (webtable 3).

Among all 28 trials, statin/more therapy compared to control/less therapy produced a 21% (RR 0.79; 95% CI 0.77-0.81) proportional reduction in the risk of a first major vascular event per 1.0 mmol/L reduction in LDL cholesterol. There were independently significant risk reductions in each of the age groups considered, including among patients aged over 75 at the start of treatment. Although the proportional reductions in major vascular events appeared to diminish slightly with increasing age, the trend was not statistically significant (trend $p=0.06$; figure 1(a)). It has previously been shown that statin therapy does not reduce the rate of major vascular events among patients with moderate or severe heart failure or who are undergoing dialysis for renal failure[16-19,26] (heterogeneity $p<0.0001$; figure 2). Disproportionately more patients with heart failure or dialysis were represented from these trials in the older age groups, which could confound comparisons between the effects of statin therapy by age. In exploratory analyses, after exclusion of the 13,613 (7%) patients from the four trials restricted to heart failure or dialysis patients,[17-19,26] the suggestion of a trend towards smaller proportional reductions in major vascular events with older individuals was diminished (trend $p=0.3$; figure 1(b)). These patterns were unchanged after adjustment for gender, diabetes, hypertension, smoking, prior CVD status, BMI and renal function (adjusted p for trend = 0.06 in 27 trials with individual participant data; $p=0.4$ after excluding four trials that exclusively included participants with heart failure or on dialysis).

Overall, statin/more therapy yielded a 24% (RR 0.76; 95% CI 0.73-0.79) proportional reduction in major coronary events per 1.0 mmol/L reduction in LDL cholesterol. There was a statistically significant trend towards smaller proportional reductions in major coronary events with increasing age (trend $p=0.009$; figure 3), which remained significant after excluding the heart failure and dialysis trials (trend $p=0.01$; webfigure 1). As for the analyses of major vascular events, these

patterns were unchanged after adjustment for gender, diabetes, hypertension, smoking, prior CVD status, BMI and renal function (adjusted p for trend = 0.008 in 27 trials with individual participant data; p=0.012 after excluding four trials that exclusively included participants with heart failure or on dialysis). Even among patients aged over 75, however, there was still a significant reduction in major coronary events. When comparisons were made between patients aged ≤75 or >75 years, there were no significant differences between the proportional effects on major coronary events, or on nonfatal myocardial infarctions and coronary deaths considered separately (with or without exclusion of the heart failure or dialysis trials; webfigure 2).

Overall, there was a 25% (RR 0.75; 95% CI 0.73-0.78) proportional reduction in the risks of coronary revascularisation procedures with statin/more therapy per 1.0 mmol/L lower LDL cholesterol, which did not differ significantly across age categories (trend p=0.6), although there was no apparent effect on the relatively small number of procedures performed among patients aged >75 years (figure 3 and webfigure 1). Similarly, the proportional reductions in stroke of any type (RR 0.84; 95% CI 0.80-0.89) did not differ significantly by age group (trend p=0.7; figure 3).

Among participants with known vascular disease at study entry, the proportional reductions in major vascular events were similar irrespective of age, regardless of whether heart failure and dialysis trials were included or excluded (trend p=0.2 and 0.9 respectively; figure 4 and webfigure 3). However, among participants with no history of vascular disease, there was a weakly significant trend towards smaller proportional risk reductions with increasing age (trend p=0.05; figure 4) that persisted after excluding the heart failure and dialysis trials (trend p=0.03; webfigure 3).

Overall, there was a 12% (RR 0.88; 95% CI 0.85-0.91) proportional reduction in vascular mortality per 1.0 mmol/L reduction in LDL cholesterol, with a trend towards smaller proportional reductions with older age (trend p=0.004; Figure 5(a)). However, 53% (n=1014) of the vascular deaths among people aged >75 occurred in the four heart failure or dialysis trials. After exclusion of those trials, there was no apparent trend towards smaller proportional reductions in vascular mortality with older age (p=0.2, figure 5(b)). There was no effect of statin therapy on all non-vascular causes of death (RR 0.96; 95% CI 0.92-1.01) irrespective of age group (trend p=0.7; webfigure 4). Nor were there any adverse effects on deaths due to cancer, or on the larger numbers of incident cancer cases, by age (webfigure 5). Consequently, when the beneficial effect on vascular mortality and the lack of effect on non-vascular mortality was combined, there was a significant reduction in all-cause mortality (RR 0.91; 95% CI 0.88-0.93). As for vascular mortality, there was a trend towards smaller proportional

reductions in all-cause mortality with increasing age (trend p=0.04, webfigure 6(a)), but this did not persist after excluding the heart failure and dialysis trials (trend p=0.1, webfigure 6(b)).

Discussion

Individual randomised trials of statin therapy have previously reported significant cardiovascular risk reductions among participants aged >65-70 years at the time of randomisation (who were therefore aged >70-75 years at the end of an average of five years of scheduled treatment).[27-31] Meta-analyses of the results among older people have consistently reported evidence for beneficial effects in secondary prevention, but the evidence has been less clear in primary prevention.[32-35] The availability of individual participant data in the CTT Collaboration database [21]has permitted more detailed assessment of the effects of statin therapy at different ages.

In this meta-analysis of data from 28 trials among nearly 187,000 people (with about 14,500 aged over 75 years at randomisation), there was a tendency towards slightly smaller proportional risk reductions in major vascular events (trend p=0.06) and vascular deaths (p=0.003) with increasing age. The exclusion criteria for 24 of these trials incorporated at least one of: a history of heart failure, poor ejection fraction, poor prognosis (other than from atherosclerotic disease) or the requirement for renal dialysis. However, two of the trials were conducted specifically in patients with moderate to severe (New York Heart Association (NYHA) Class II-IV) heart failure[17,18] and two in patients with end-stage renal disease requiring dialysis.[19,26] Statin therapy has not been shown to reduce the risk of major vascular events or vascular deaths in either of these patient populations,[16-19,26] and consequently is not recommended for such patients in the absence of other indications.[10,36,37] We therefore conducted exploratory analyses that excluded these 4 trials[17-19,26] in order to assess their contribution to the observed trends towards smaller relative reductions with increasing age. These analyses showed that, among people without heart or renal failure, there was little evidence of any diminution of the beneficial effect on major vascular events or on vascular deaths with increasing age (trend p=0.3 and 0.2 respectively).

The proportional reductions in major vascular events also appeared to be similar irrespective of age among patients with a history of vascular disease (ie, secondary prevention), but there was a trend towards smaller proportional risk reductions in those with no known vascular disease (ie, primary prevention), with no independently significant reductions observed among the those >70 to ≤75 or >75 years of age. Only about one fifth of the major vascular events contributing to these analyses

occurred among individuals without a history of vascular disease, and this relative paucity of evidence has led to further primary prevention trials being conducted, particularly among older individuals. For example, the STAREE trial aims to assess the effects of atorvastatin 40mg daily in 18,000 primary prevention patients aged ≥70 years at the time of recruitment.[38]

There was a trend towards smaller proportional reductions in major coronary events (p=0.01) with increasing age, although there was still a significant reduction among the patients aged over 75 years at randomisation. The reasons for this trend are unclear. Age related factors - such as altered pharmacokinetics and pharmacodynamics, and a higher risk of drug interactions in the setting of polypharmacy[39] – would be expected to influence absolute LDL cholesterol reductions from therapy, but these did not differ materially by age. The trend may reflect a reduced capacity for statins to impact on advanced atherosclerotic plaques, greater diagnostic uncertainty at older ages (eg, difficulty separating myocardial infarctions due to unstable atherosclerosis from supply-demand imbalances that occur with other illnesses), and poorer long-term adherence with the assigned study treatment among older people (since our weighted analyses are based on one year LDL cholesterol differences). There were no trends towards smaller proportional reductions in coronary revascularisation procedures or strokes with increasing age, but too few such events occurred among patients aged over 75 to assess the effects on these outcomes directly. Statin therapy definitely decreases the risk of ischaemic stroke and any stroke overall, but may increase the risk of haemorrhagic stroke.[14] Individual participant data were not available from one eligible trial[22] in which a large number of strokes (especially haemorrhagic) occurred, and it is not currently possible to comment reliably on the relevance of age to the effects of statin therapy on stroke subtypes.

There is limited information on the effects of statins on mortality in people at low risk of vascular disease, and very large trials (eg, the ongoing STAREE trial[38]) would be needed to provide direct evidence of a mortality reduction among older people in primary prevention. However, our overall analyses in a combined primary and secondary prevention population indicate that the proportional reductions in vascular mortality are similar irrespective of age. We have previously shown that statin therapy does not increase the incidence of cancer[15] (as had been suggested[8]) or of non-vascular causes of death.[14] Consequently, given the similar proportional reductions in vascular mortality in both primary and secondary prevention settings, and the lack of effect of statin therapy on non-vascular mortality, reductions in total mortality would be expected in both clinical settings.

Statins have been estimated to increase the risk of myopathy (defined as muscle pain or weakness combined with large increases in blood concentrations of creatine kinase) typically by 1 case per 10,000 statin-treated patients per year,[9] but this risk can be increased by drug interactions and major comorbidities that are more common in older people.[40] A meta-analysis of published data for participants aged ≥65 years at randomisation in statin trials reported no increased risks of less severe muscle-related adverse events.[41] Currently the CTT is undertaking a pre-specified analysis of reported adverse events in statin trials from original trial records,[42] including examining whether age directly influences the small increase in risk of diabetes,[43,44] and whether statins adversely influence cognition (noting that no excess risks have been identified in any large randomised trials[30,31,45,46])

The selection criteria used among the 28 trials contributing to this meta-analysis, as well as differences in when they were conducted, mean that the absolute risks of major vascular events and mortality in our overall study population are not likely to be representative of any contemporary population. For that reason, we have not produced estimates of the absolute effects of statin therapy directly from the event rates observed in these trials. By contrast, the proportional effects observed in the meta-analysis are likely to be widely generalizable. Consequently, given that the proportional reductions in major vascular events appeared to diminish only slightly (if at all) with increasing age, while untreated absolute risks of major vascular events in the general population increase exponentially with age, the absolute benefits of a given absolute reduction in LDL cholesterol with statin therapy would be expected to be substantially greater among older individuals. For example, in the primary prevention setting, two individuals aged 63 or 78 years with otherwise identical risk factors might be expected to have major vascular event rates of 2.5% versus 4.0% per annum respectively. Reducing those risks by one-fifth with a 1.0 mmol/L LDL cholesterol reduction would prevent first major vascular events from occurring each year in 50 and 80 individuals respectively per 10,000 treated.

In conclusion, statin therapy produces significant reductions in major vascular events irrespective of age. There is less definitive direct evidence of benefit in the primary prevention setting among patients aged over 75, but the totality of evidence supports the use of statin therapy in older people considered to be at a sufficiently high risk of having occlusive vascular events.

Contributors:

Establishing collaboration: AK, CB, JS, RC. Study concept: AK, JF, BM, CB, RC, JS. Data collection: RC, CB, CR, JE, LB, AK, JS, EB. Analysis specification and interpretation: AK, JF, BM, JE, CB, RC, JS.

Statistical analyses and figures: BM, ROC, JF, LB. First draft manuscript: AK, JF. Revision: all authors. All collaborators had an opportunity to contribute to the interpretation of the results and to drafting of the report. AK, JF, BM, CB had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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Research In Context Panel - Revised

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Efficacy and safety of LDL-lowering therapy in older people: meta-analysis of data from 187,000 participants in 28 randomised controlled trials

Cholesterol Treatment Trialists' (CTT) Collaboration

Main tables and figures

Page

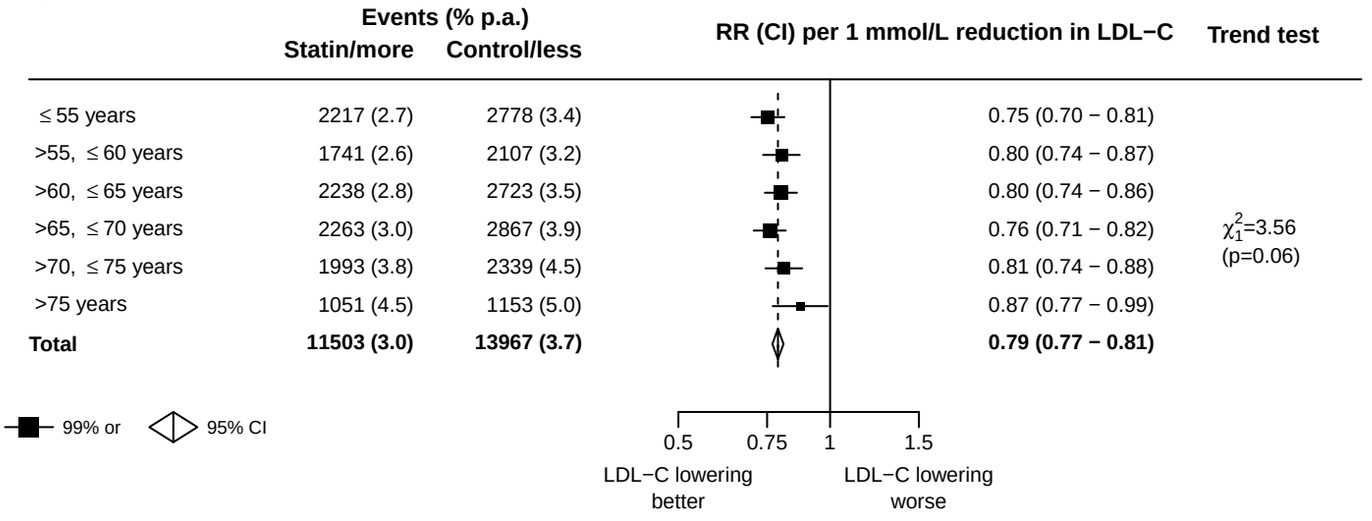
Table 1: Baseline characteristics of participants in all studies

	Age at randomisation, N(%)*	
	≤75	**>75**
Number of people	172,321	14,483
Age (years)	61.5 (8.3)	78.8 (3.0)
Male	125,783 (73%)	8,476 (58%)
History of vascular disease	96,088 (56%)	8,034 (55%)
History of myocardial infarction	59,654 (35%)	4,210 (29%)
History of other symptomatic coronary heart disease	61,767 (35%)	4,448 (31%)
History of heart failure (NYHA class II-IV)†	6,692 (4%)	2,893 (20%)
On dialysis‡	3,546 (2%)	482 (4%)
History of diabetes	31,919 (19%)	2,499 (17%)
Current smokers	35,701 (21%)	1,485 (10%)
Treated hypertension	82,213 (49%)	8,698 (60%)
Systolic blood pressure (mmHg)	138.1 (20.9)	143.4 (23.0)
Diastolic blood pressure (mmHg)	81.2 (11.3)	78.9 (11.6)
Body mass index (kg/m²)	27.1 (24.6-30.1)	26.3 (23.8-29.1)
Total-cholesterol (mmol/L)	5.4 (1.1)	5.1 (1.1)
LDL-cholesterol (mmol/L)	3.4 (1.0)	3.2 (1.0)
HDL-cholesterol (mmol/L)	1.2 (0.4)	1.3 (0.5)
Triglycerides (mmol/L)	1.6 (1.2-2.2)	1.4 (1.0-1.9)
Creatinine (µmol/L)§	94 (80-106)	99 (88-117)

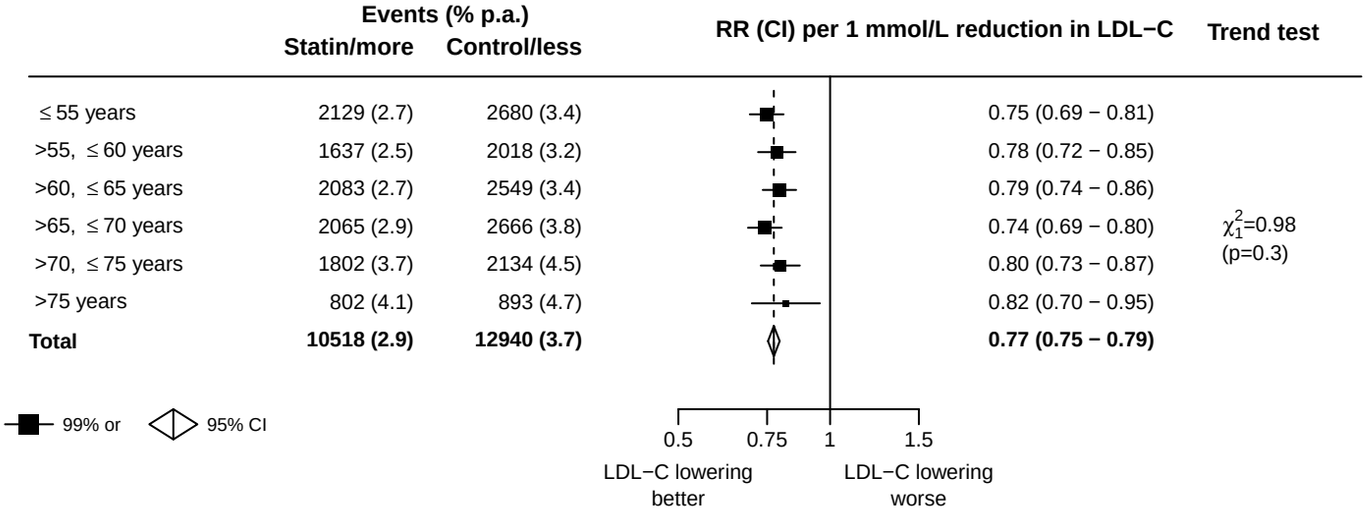
Data presented as number of participants (%), mean (SD) or median (IQR). HOPE-3 participant data for body mass index (mean (SD) 27.21 (4.77) among ≤75 and 26.14 (4.78) among >75 year old participants), triglycerides (149.02 (94.14) and 140.07 (78.14), respectively) and creatinine (0.89 (0.21)); and 0.93 (0.23), respectively) not included.*Excludes 50 participants with missing age (49 from MEGA and 1 from A to Z). †All participants from GISSI-HF and CORONA trials only. ‡All participants from 4D and AURORA trials. §Excludes participants on dialysis at randomisation (ie, participants from 4D and AURORA).

Figure 1: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by age at randomisation

a) All studies

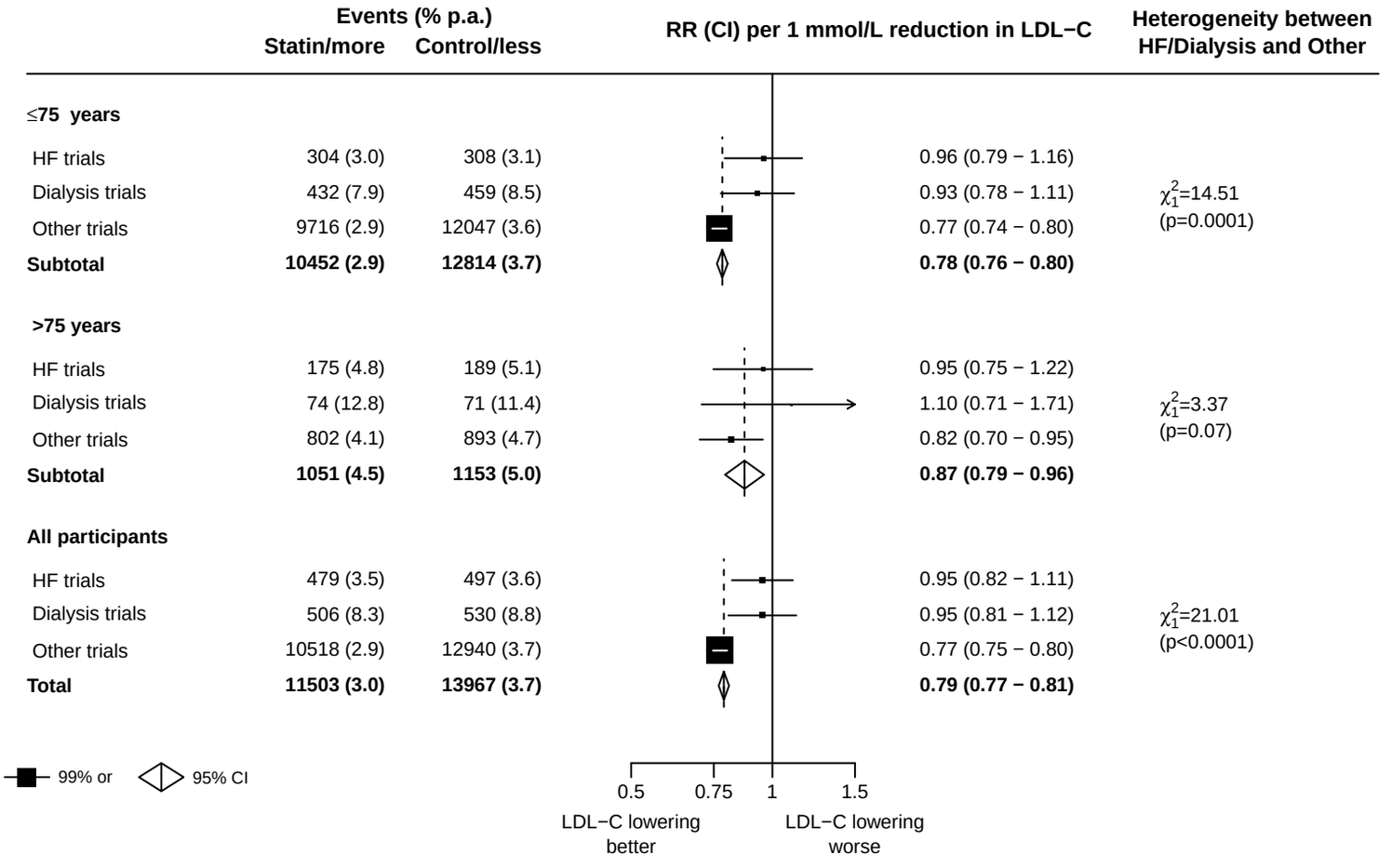


b) Excluding four trials that exclusively included participants with heart failure or on dialysis



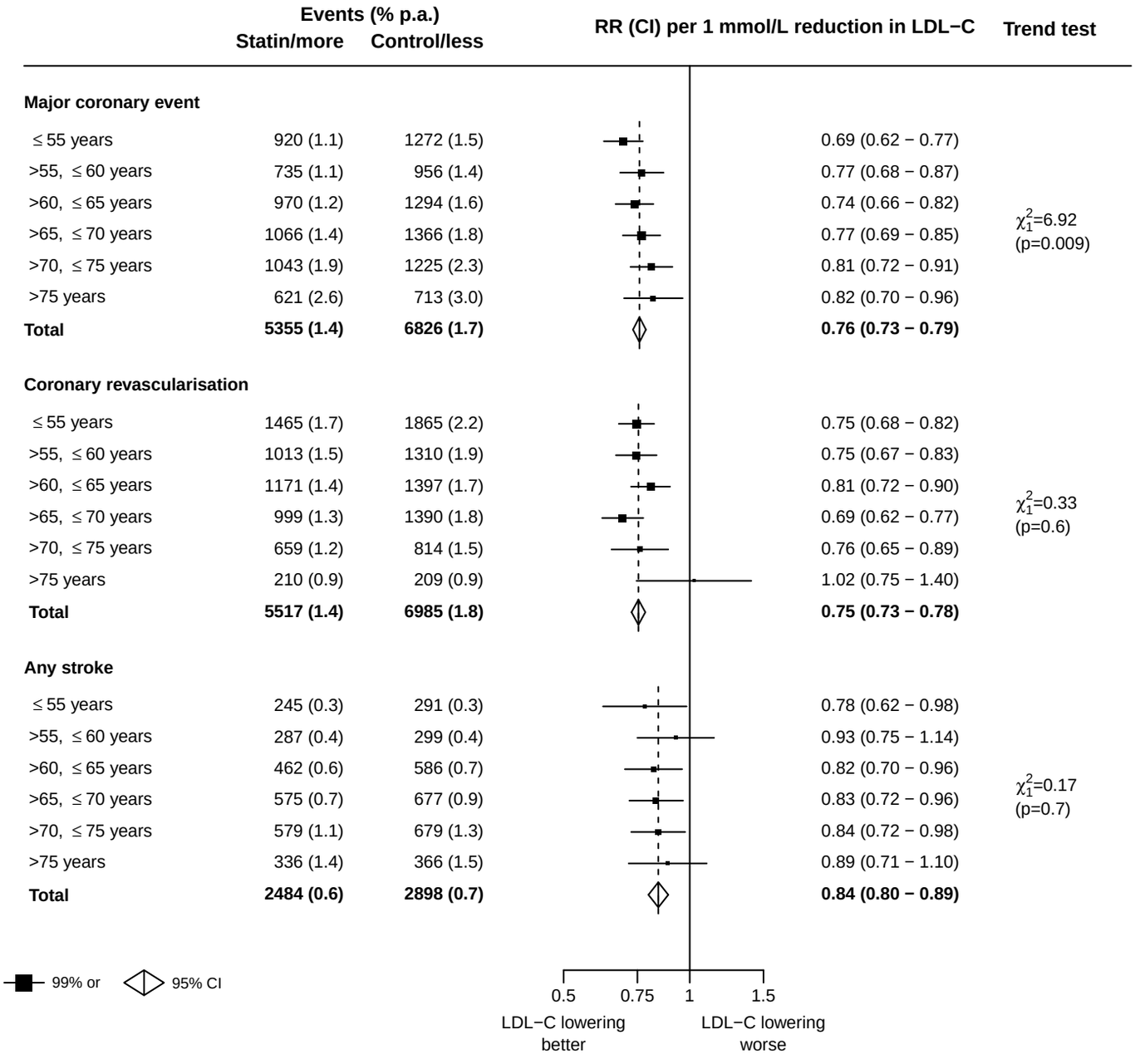
Data on participants with missing baseline data included in totals.

Figure 2: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, subdivided by age at randomisation and particular trial populations



Data on participants with missing baseline data included in total.

Figure 3: Effects on components of MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol in all studies, by age at randomisation



Data on participants with missing baseline data included in totals.

Figure 4: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, subdivided by age at randomisation and by prior vascular disease

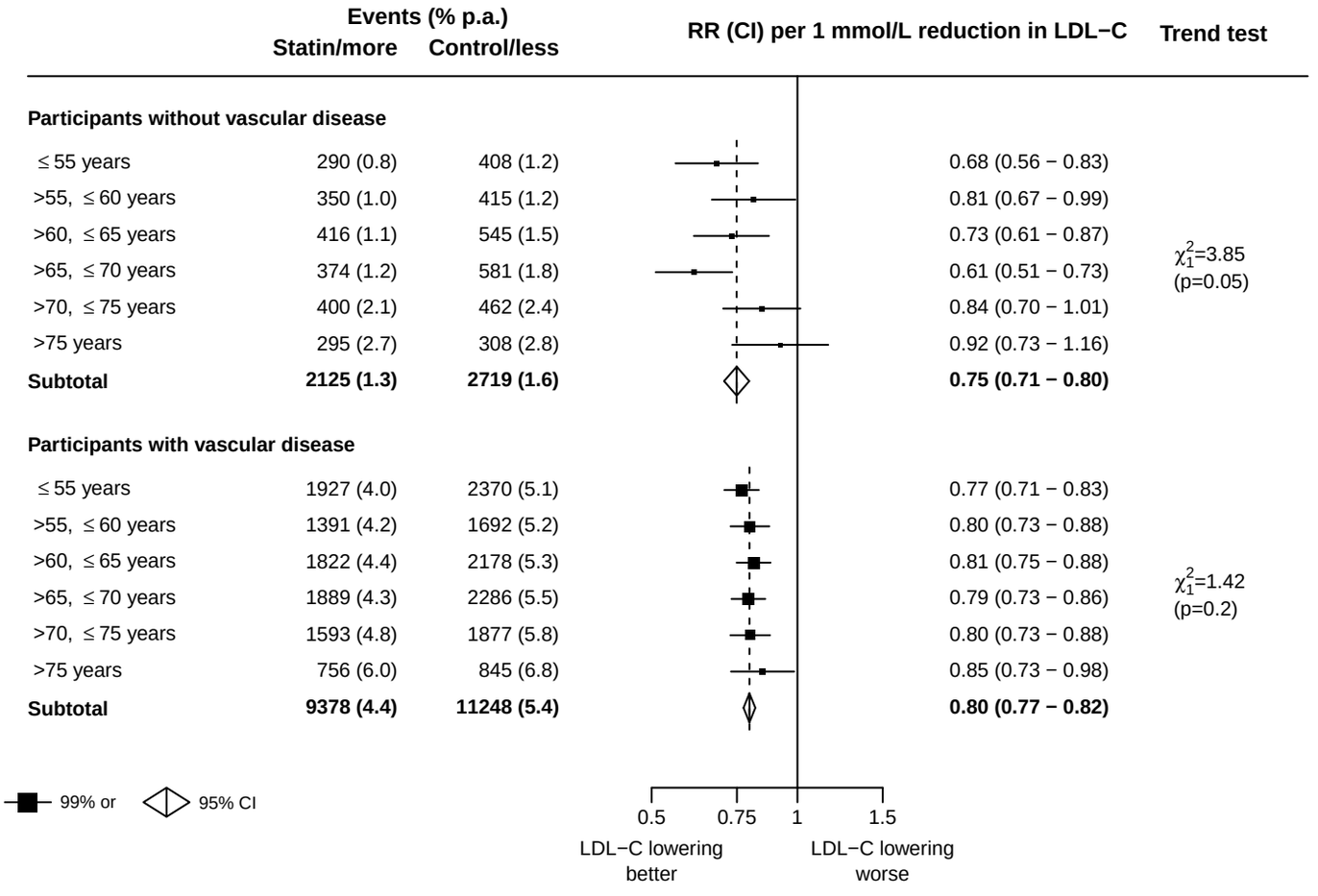
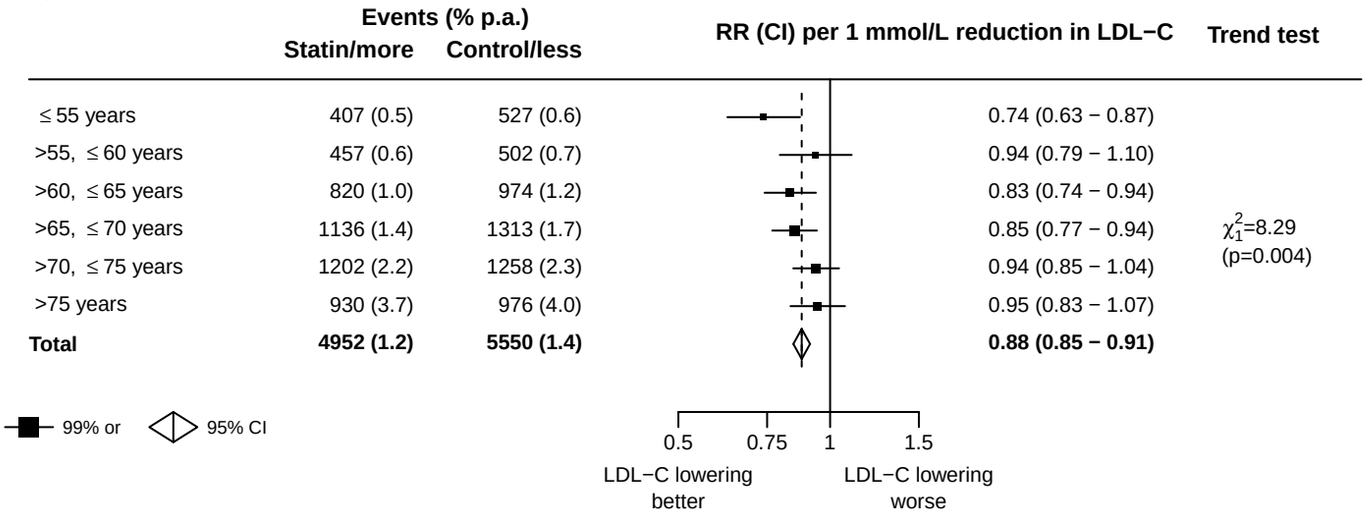
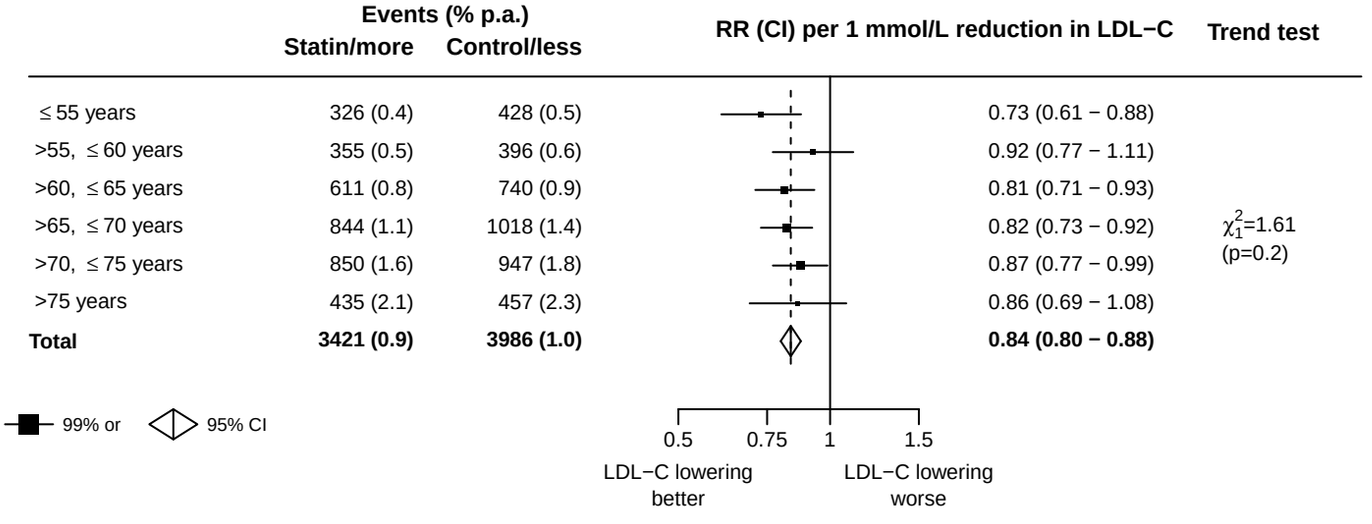


Figure 5: Effects on VASCULAR DEATH per mmol/L reduction in LDL cholesterol, by age at randomisation

a) All studies



b) Excluding four trials that exclusively included participants with heart failure or on dialysis



Data on participants with missing baseline data included in totals.

Supplementary Material

Click here to download Web Appendix: CTTelderlyall-1-12-2017 supplFigtables.pdf